Decision Memo for Liver Transplantation for Malignancies (CAG-00091N)

Decision Summary

Our review of the scientific evidence indicates that liver transplantation in patients with HCC is reasonable and necessary in selected patients. Specifically, we evaluated patients for who transplant is treatement for HCC and patients transplanted for other reasons who are found to have HCC. There are a number of retrospective comparison studies that demonstrate that both actuarial survival and recurrence-free survival in groups of patients with HCC treated with transplantation achieve results comparable to non-malignant transplant cases. Generally, we would prefer to have prospective comparative studies on which to base our determination. However , given the life-threatening nature of HCC for patients who are not eligible for liver resection, we believe there may be legitimate ethical concerns surrounding randomization of patients for a prospective trial of this procedure. While the existing retrospective studies may have allowed for some selection bias in the form of the HCC patients undergoing transplant, some studies adjusted for this possibility. In addition, the studies clearly demonstrate that properly selected HCC patients have good long-term outcome following transplant. Thus, we believe that there is sufficient evidence in this case to support a NCD for adult liver transplantation for HCC in specific circumstances.

Through the literature we reviewed, several patient characteristics were found to strongly predict outcome in liver transplant patients. Thus, this decision memorandum announces Medicare's intention to make a national coverage decision for liver transplantation for patients with HCC only under the following circumstances:

- The patient is not a liver resection candidate;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and,
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

Most of the literature we reviewed explicitly stated that liver transplant should be reserved for those patients for whom liver resection is not an option primarily due to poor liver function or location of the tumor. Unlike patients with liver resection, patients receiving liver transplantation are on a lifetime regimen of immunosuppression, which presents ongoing health risks, such as increased risk of infections. Because of these risks associated with liver transplantation we do not believe transplantation is reasonable and necessary when liver resection is likely to produce a comparable result.

Virtually all of the literature we reviewed identified tumor size greater than 5 cm as an adverse risk factor for liver transplantation for HCC. While many of the researchers noted an association between tumor size and negative outcomes, Klintmalm, Figueras et al.(1997) and Iwatsuki et al.found tumor size as a significant variable in predicting outcome. In their most recent research, Iwatsuki et al. determined that a patient with tumors greater than 5 cm is 6.7 times more likely to have a low chance of survival at 5 years.

The UNOS criteria consider tumor size in determining the status of patients on the wait list. Patients with a single tumor less than 5 cm or 3 or fewer tumors all less than 3 cm may be considered as a Status 2B candidate on the list. Patients with larger tumors may only be considered as a Status 3 candidate and will have a significantly reduced chance of being allocated a donated liver. Given the evidence linking tumor size with poor outcomes, we do not believe that it is reasonable or necessary to perform liver transplants on patients with tumors greater than 5 cm.

From the evidence we reviewed in analyzing liver transplantation for HCC, the most consistently discussed significant adverse prognostic factors were macrovascular invasion and extrahepatic spread. Figueras et al., Iwatsuki et al. and Klintmalm all found these factors to be a significant negative influence on the likelihood of survival especially for disease free survival. Iwatsuki et al. found that transplantation of patients with macovascular tumor invasion increased their risk of poor outcome by a factor of 15 times. Hepatocellular carcinoma that invades the vascular system is more likely to recur and effect the grafted liver. Similarly, the UNOS criteria for Status 2B include a condition that patients be evaluated to "rule out any macrovascular involvement." We have concluded that the evidence supports a determination that liver transplantation for HCC with macrovascular invasion is not reasonable and necessary given the magnitude of the risks for recurrence.

The researchers likewise found extrahepatic spread of HCC significantly affected the outcome of liver transplantation as a means of curing HCC. Iwatsuki et al., Klintmalm, Mazzaferro et al. and Yamamoto et al. all identified extrahepatic spread as a factor that negatively effected the outcome of liver transplantation. Iwatsuki et al. found recurrence of cancer in these patients to be universal within 2 years of transplantation . Klintmalm identified extrahepatic spread as an independent variable in his regression analysis and Mazzaferro et al. identified this as the only significant factor in his analysis. UNOS status 2B criteria specify that extrahepatic spread is to be ruled out. Given the strong evidence for rapid recurrence of cancer in patients with extrahepatic spread, we concluded that the likelihood of risks that exceed benefits for patients in this category is high. Therefore, we have concluded that liver transplantation where there is evidence of extrahepatic spread is not reasonable and necessary.

Several researchers have identified tumor number and staging as adverse factors. Further, the UNOS status 2 B criteria are limited to patients with Stage I or Stage II tumors in accordance with the Tumor-Node-Metastasis (TNM) classification system. This results in Status 2 B classification only to patients with 3 or fewer nodules. We considered use of tumor numbers and staging as independent factors in establishing our conditions for coverage in the decision memorandum. However, we found that many of the researchers did not study or find any negative relationship between tumor number and outcome. Of those researchers that did study this variable, all found a negative association, but failed to identify it as being statistically significant.

More researchers studied tumor staging as a variable. Similar to tumor number, the researchers consistently found a negative association of outcome with higher staging. That is, as the stage of the tumor increased, the disease-free survival of the patients decreased. But only one researcher, Klintmalm, in his 1998 work, found this association to be statistically significant. Given the high likelihood of occurrence of other significant adverse factors, such as increased tumor size, macrovasularization and extrahepatic spread, to occur in patients with higher stage tumors, it is possible that these other factors are the cause of the negative association of increased staging with outcomes. Therefore, we have not included these factors in our conditions for coverage in the decision memorandum.

In addition, several researchers found a negative association with outcomes for bilobar distribution and microvascularization. However, the only factor identified as statistically significant was bilobar distribution in the Iwatsuki et al. study in 1991. In Iwatsuki's later research, he empirically weighted these risk factors as 3.1 for bilobar distribution and 4.4 for microvascularization. We note that the UNOS status 2 B criteria do not consider either of these factors. Further, identification of microvascularization prior to transplantation requires the use of a biopsy procedure that, in and of itself, may be an adverse risk factor in patients with HCC in that the procedure may seed the tumor. Thus, we concluded that a link between these factors and poor outcomes is unlikely. Consequently, we did not exclude patients with these conditions from our conditions for coverage in the decision memorandum.

In summary, we have decided to issue this decision memorandum announcing our intention to revise the NCD relating to liver transplantation for malignancies. We will issue a revision to the Coverage Issues Manual stating that liver transplantation may be covered for patients with HCC when the following conditions are met:

- The patient is not a liver resection candidate;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

Liver transplantation for other malignancies continues to be excluded from coverage at this time. We will, however, seek a technology assessment on these other types of malignancies.

HCFA's coverage policies are updated as new scientific information becomes available. We welcome comments on this document now or in the future. In addiiton, HCA will accept a request for reconsideration of this decision memorandum or any NCD if there is felt to be a Federal misinterpretation of existing evidence or if new evidence is provided that may alter the conclusion of this assessment.

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Decision Memo

TO: File: Liver Transplantation for Patients with Malignancies
CAG-00091N

FROM:

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RE: National Coverage Determination Request
DATE: May 21, 2001

This memorandum serves four purposes: (1) outlines the description and treatment of liver malignancy with particular emphasis on the role of transplantation, (2) reviews the history of Medicare coverage policies on liver transplantation and provides a timeline of recent activities, (3) presents and analyzes the relevant scientific data related to the use of liver transplantation for malignancies, and (4) delineates the reasons supporting a change in the national coverage determination (NCD) for this therapy.

Clinical Background

Malignancy of the liver is not a homogeneous clinical condition. There are a variety of malignancy types that affect the liver, such as metastatic disease, hepatocellular carcinoma, bile duct carcinoma, and epithelioid hemangioendothelioma, among others. Further, for a given tumor type there are a number of characteristics, such as size, lobar distribution, vascular invasion, etc., that describe the tumor in a particular patient. In the United States, metastatic carcinoma to the liver is much more common than primary hepatic malignancy.

In adults in this country, hepatocellular carcinoma (HCC) accounts for 80-90 percent of primary hepatic cancers.[1] The disease afflicts males far more often than females. Although many factors may lead to HCC, the disease is usually limited to those persons with preexisting liver disease. Approximately 60 to 80 percent of patients in the United States with HCC have a cirrhotic liver, and more than 10 percent of individuals with cirrhotic liver eventually develop HCC. The risk appears highest in patients whose liver disease is caused by inherited hemochromatosis or hepatitis B or C viral infection. Other causes of cirrhosis that can lead to HCC include alcohol abuse, schistosomal infestation, homozygous alpha-antitrypsin deficiency, and hepatic fibrosis caused by chronic administration of methotrexate. [2]

The apparent synergism of chronic liver injury and persistent viral infection in the development of HCC is in keeping with the multi-step hypothesis of carcinogenesis in HCC, requiring both initiating and promoting events. The activation of protooncogenes and inactivation of suppressor genes increase as hepatocytes replicate. Adenomatous hyperplasia or dysplastic nodules result from genetic alterations, are monoclonal and are felt to be the first step in the evolution of malignancy. Subsequent genetic changes lead from dedifferentiation to well-differentiated HCC, and subsequently to poorly-differentiated HCC over a period of months to years.[3]

The stage of the malignancy and the severity of the underlying liver disease are important factors in determining suitability for any treatment. Preoperative histologic confirmation of HCC is not required in most cases, particularly if alpha-fetoprotein (AFP) levels are diagnostic, partly because of fear of needle track seeding associated with needle biopsy. Ultrasound, computed tomographic scanning and magnetic resonance imaging are generally used to identify the size of lesions, their relationship with vessels, and to differentiate HCC from other small-mass lesions in a nodular cirrhotic liver. The high incidence of HCC in a population in which chronic hepatitis is endemic has led to the introduction of formal screening programs to identify patients with HCC at an earlier stage.

Up to 40% of HCC in transplant patients is "incidental," being detected only during pathologic examination of the excised organ after surgery.[4] This rate of incidental HCC decreases with improved imaging technology, but probably remains about 25% in the best of circumstances.

Multiple nonsurgical approaches to the treatment of HCC have been undertaken for both early and advanced disease. Recent results of percutaneous ethanol injection (PEI) in HCCs smaller than 3 cm show complete necrosis of tumor in up to 90% of patients. Other methods of local destruction including cryotherapy and radiofrequency ablation have also shown similar results. A number of other modalities have also been advocated, including arterial embolization, chemoembolization, systemic chemotherapy, intrahepatic arterial chemotherapy, radiotherapy, immunotherapy, and hormonal manipulation. [5]

Potentially curative surgical options consist of either partial hepatic resection or total hepatectomy with liver transplantation. The considerations in deciding on resectability of a primary liver cancer are general health status of the patient, tumor stage, and functional capacity of the underlying liver. Data show that Stage IIIB or IV disease is incurable by resection. (See attachment 1 for description of tumor staging.) For example, Onodera et al. found that no patient in stage III or IVB survived for more that 4 years.[6] Ikai et al. found no patients with tumor thrombi in the inferior vena cave survived more than 2 years and 5-year survival rates for all stage IV-A HCC were at 20 percent or less.[7] Other factors thought to be predictors of poor outcome for resection include multiple tumors, large size, and vascular invasion. The anatomical location of a lesion may also make it technically unresectable, even if its staging were favorable.

One of the most difficult aspects of assessment of resectability is determination of the functional reserve of the liver, which is the ability of the liver to tolerate an anesthetic and operative procedure and to regenerate after removal of part of its functional mass. The risk of poor outcome following resection is higher in cirrhotic than non-cirrhotic patients.

An alternative to partial resection of the liver is total hepatectomy with transplantation from a cadaveric or living source. Due to the shortage of cadaveric liver donors, transplantation has generally been reserved for those patients whose residual liver function is so poor as to make the probability of successful resection very low.

History of Medicare's Coverage of Liver Transplantation

Transplantation is the preferred and essentially only curative treatment for end-stage liver disease. Medicare first issued a national coverage policy on liver transplantation in 1984. This initial policy limited coverage of liver transplantation to pediatric patients (under age 18) with extrahepatic biliary atresia or any other form of end-stage liver disease, except that coverage was not provided for children with a malignancy extending beyond the margins of the liver or those with persistent viremia. Following review of an August 14, 1989, technology assessment report conducted by the Office of Health Technology Assessment in the Public Health Service, HCFA published a notice in the *Federal Register* (56 FR 15006) on April 12, 1991 expanding Medicare coverage of liver transplantation to adults with one of the following conditions: primary biliary cirrhosis; primary sclerosing cholangitis; postnecrotic cirrhosis due to hepatitis B surface antigen negative; alcoholic cirrhosis; alpha-1 antitrypsin deficiency disease; Wilson's disease; or primary hemochromatosis. In addition, HCFA limited Medicare coverage to transplants performed in qualifying facilities.

The *Federal Register* Notice specified the criteria for approval of transplant centers to perform Medicare covered liver transplants. Criteria include: facility's patient selection policies, patient management protocols, commitment of resources to the transplant program, facility plans for continued performance, experience and survival rates, maintenance of data, and laboratory services. Medicare coverage was effective with the date of the transplant center's approval. The earliest date of approval for liver transplantation in adults was March 8, 1990.

In June 1993, a committee of physicians from various Government agencies and Medicare contractor medical directors considered expanding the diagnoses for Medicare coverage of liver transplantation at the request of the University of Pittsburgh Medical Center. The committee recommended that HCFA examine the current literature and solicit expert opinion to determine whether Medicare should change its current policy of covering liver transplantation for specific conditions to covering liver transplantation for patients with any form of end-stage liver disease, with certain exceptions. Malignancy was specifically noted as one of the exceptions contemplated.

HCFA staff reviewed the medical literature and analyzed data from both the Scientific Registry of Transplant Recipients (transplants performed in the United States). We also analyzed HCFA's internal database generated from information submitted with applications from transplant centers applying for Medicare approval. The information showed that patients being transplanted for malignancies and hepatitis B had significantly poorer long-term survival outcomes as compared to patients transplanted for other end-stage liver diseases. Analysis of data from the institutions that applied to HCFA to be approved for coverage of liver transplants showed 5-year survival among patients with malignancy was 33.6 percent, compared with 70 to 80 percent among patients with six of the seven non-malignant conditions initially covered by Medicare.[8] HCFA determined that the literature supported expansion of coverage of transplants for end-stage liver disease, but not for malignancy. Effective July 15, 1996, Medicare coverage of liver transplantation was expanded to include all end-stage adult liver disease except hepatitis B or malignancies. The NCD was further expanded on December 10, 1999 to include coverage for individuals with hepatitis B. (See Coverage Issues Manual 35-53.)

More recently, HCFA has become aware of published studies showing that outcomes for patients undergoing transplant and having HCC may not be as poor as believed. We decided to internally generate a NCD request to determine whether new literature supports a change in our coverage policy. We posted notice of this action on www.cms.hhs.gov/coverage on February 13, 2001.

Methods

We began our analysis of this issue with a search of the medical literature. It seemed clear from the brief survey of literature we conducted prior to initiating the request that there was a significant difference in the quality of the evidence regarding HCC as opposed to other liver malignancies. In an effort to avoid delaying a Medicare coverage decision on HCC, we decided to separate the issues. We intend to seek a technology assessment on the issue of liver transplantation for forms of liver malignancy other than HCC.

We used MEDLINE through OVID to conduct our primary literature search. For purposes of this review, therefore, we limited our search to MeSH headings found using the following search terms: English language articles, 1993 publication or later, liver transplantation, hepatocellular carcinoma, disease-free survival, and graft survival. We reviewed approximately 75 abstracts obtained by combining the above subject terms. We excluded articles where HCC was not the primary topic, those that primarily analyzed pre-transplant treatment, and those analyzing post-transplant graft loss, such as rejection. We also excluded small (less than 10) case series studies and those with only short-term (less than 1-year) outcomes. We selected 22 articles, capturing all those that included comparative data on long-term outcomes between transplant and other treatment options for HCC. (See bibliography and evidence chart attached to this decision memorandum.) In addition, as a result of our Internet posting, we received an additional article that was not yet published, which we reviewed in the development of this decision memorandum. There were no randomized prospective clinical trials in the literature. The articles we selected were case series and retrospective comparison studies.

In addition to the published scientific literature, we reviewed the policy guidelines developed by the United Network for Organ Sharing (UNOS) related to liver transplantation. These policies were developed by a consensus of the members of UNOS and are nearly universally adhered to among its members. We further solicited from the Scientific Registry outcome data on liver transplantation for patients with malignancy as the reason for transplant, and patients with incidental malignancies compared to overall outcomes for liver transplants as reported to the registry.

Summary of Evidence

A. Literature Review

In the late 1960s and 1970s liver transplantation was viewed with enthusiasm and used for patients with advanced HCC in large part because there were no alternative therapies that offered any hope of cure. This enthusiasm changed to pessimism in the 1980s and early 1990s, when the modest, if not bleak, aggregate, long-term survival following transplantation with any HCC was recognized. In that era of pessimism surrounding transplantation for HCC in general, some investigators began to study the association between tumor characteristics and outcome. Evidence grew that careful patient selection resulted in survival that approached or equaled that for patients without HCC.

The following two questions, along with pertinent recent evidence, frame this formulation and assessment for liver transplantation and HCC:

1. Is the survival rate of patients with HCC and cirrhosis who undergo liver transplantation approximately the same as the survival rate of transplant patients with cirrhosis alone?

- Figueras et al.[9] conducted a prospective cohort study that reported survival in cirrhotic patients who received transplants from 1990 through 1995 (median follow up for cirrhotic group was 26 months and 24 months) for HCC group . They studied 38 patients with HCC and 136 with no pre-operative or pathologic evidence of malignancy. Actuarial 5-year survival was 63% in those patients with HCC and 68% in those without (p=.84).
- Min et al.[10] reviewed the records of 55 patients transplanted for hepatitis C virus (HCV) cirrhosis between November 1990 and December 1996 (median follow up 23 months), in which there was accompanying HCC, and compared them with 55 age/gender-matched HCV cirrhotic patients without HCC. Kaplan-Meier curves for both graft and patient survival showed no significant difference between these groups. However, please note the lack of case severity adjustments, as only approximately half of the HCC cases were detected prior to transplant. This perhaps suggests some selection bias in favor of healthier cases.

These two articles provide evidence that concomitant HCC does not decrease transplantation survival rates when compared to the survival rates of patients with cirrhosis only.

2. Is liver transplantation as effective as other treatment options for HCC?

- In 1991, Iwatsuki et al.[11] reported on 181 patients with HCC not associated with cirrhosis between 1980 and 1990 (median follow up 53 months for resection group; 37 months for transplant group). One hundred five patients were treated by liver transplantation and 76 were treated with resection. They found no difference in survival between the transplantation and resection groups. They concluded that liver transplantation is the treatment of choice for HCC confined to the liver when the hepatic functions are poor and/or the HCC cannot be removed by subtotal hepatic resection.
- Colella et al.[12] observed 533 HCC patients between January 1989 and January 1997 (median follow up 43 months), 46 of whom did not have cirrhosis. Although results for the non-cirrhotic group were not broken out separately, there were significant survival benefits of transplantation vs. resection, transarterial chemoembolization, percutaneous ethanol injection or no treatment (i.e., natural history of disease). A particlar strength of this study is the stratification of survival analysis according to the following factors: single vs. multiple lesions, Stage I vs. Stage II, alphafetoprotein levels, viral vs alcoholic cirrhosis, and child class. This stratification is necessary for the adjustment of case severity.

The scientific literature noted above indicates that, at least for some subpopulation of patients with HCC, transplantation may be as effective or more effective than alternative therapies and that presence of HCC in patients with cirrhosis does not result in poorer transplant outcomes. Consequently, it becomes relevant to assess which prognostic factors are associated with the more appropriate selection of transplantation candidates, and the following data, along with Attachment B, provide such information:

- Mazzaferro et al. reported in a series of 48 patients who received liver transplants from 1991 through 1994 (median follow-up 26 months) and who had cirrhosis and preoperative Stage I or Stage II HCC, overall actuarial 4-year patient survival was 75% and 4-year recurrence-free survival was 83%. (Recurrence-free survival became higher than overall survival because recurrence of cancer was excluded at autopsy in some patients who died or because data were censored earlier in the calculation of recurrence-free survival.) The authors concluded that careful patient selection to avoid those with large tumors and extrahepatic involvement is critical to obtaining positive long-term results.[13]
- Figueras et al.[14] observed tumor recurrence in three transplanted HCC patients, all with either macrovascular involvement or tumors measuring >5 cm in diameter.
- In 2000, Figueras et al. published an updated report using 85 patients receiving a liver transplant for end-stage liver cirrhosis with coincidental HCC between 1990 and 1999 (mean follow-up 28 months). They found macroscopic vascular invasion was the only factor independently associated with death or recurrence after transplant.[15]
- Klintmalm analyzed the data in the international tumor registry and reported on the impact of tumor characteristics on outcome among 422 patients (mean follow up 27 months). Tumor size <5 cm, lack of vascular and lymph node invasion, and good histologic differentiation were significantly associated with improved outcome. [16]
- Bechstein et al. reported on a series of 52 patients with confirmed HCC (29% incidental) who received transplants from 1988 through 1996 (mean follow up 44 months). Actuarial 5-year survival was 79% in those with small tumors (Stages I-III) and 84% in 615 patients without HCC who were transplanted during the same period. Recurrence-free 5-year survival was 71% for the HCC group. Stage IV tumors were associated with 44% 5-year survival.[17]
- Referring again to Iwatsuki et al., poor prognostic factors were found to be multiple gross tumors, vascular invasion, advanced stage, positive surgical margins and infiltrative shape of tumor. Tumor size of more that 2 cm was a significant prognostic factor, as were bilobar involvement and lymph node metastasis.[18]
- In 2000, Iwatsuki et al. described a proposed prognostic scoring system for HCC recurrence following transplantation based on the study of 344 consecutive patients with HCC undergoing transplantation from 1981 through 1998 (median follow up 91 months). The 196 patients who had unilobar tumors less than or equal to 5 cm in diameter with no vascular invasion had actuarial 5-year tumor-free survival of 100% and 10-year survival of 95%. [19]
- Yamamoto et al. reported on 294 cirrhotic HCC patients who underwent subtotal resection in Japan compared with 270 similar patients who received liver transplants in this country (median follow-up 46 months). Survival in the transplant group was related to tumor size.[20]
- Schlitt et al. reported on 69 patients who underwent liver transplantation for HCC (minimum follow-up of surviving patients 36 months). Tumor recurrence was observed in 39 patients. Parameters associated with a higher chance of recurrence were absence of cirrhosis, tumor size greater than 5 cm, more than 5 nodules, vascular infiltration and Stage IV malignancy.

With respect to specific HCC prognostic factors, Table 1 provides a summary of literature-based findings.

B. Scientific Registry Data

The DHHS Health Resources and Services Administration under the authority of the Public Health Service Act, competitively awards a contract to an entity to maintain a Scientific Registry of Transplant Recipients. The Scientific Registry includes data on every transplant performed in the United States. In accordance with OPTN requirement 7.3, transplant centers are required to report detailed diagnostic information on patients at the time of listing for transplant, at the time of transplant, and regular follow-up periods.

At HCFA's request, the Scientific Registry reported 1, 3, and 5-year survival outcomes for liver transplant patients. The data from the Scientific Registry included 21,823 liver transplants performed between July 1, 1994 and December 31, 1999. The Scientific Registry reported 1,100 liver transplant recipients with malignancy; 677 where malignancy was the primary reason for transplant and 423 with incidental tumor found at transplant. Of those reporting malignancy as the reason for transplant, 493 reported HCC as the type of malignancy.

The Scientific Registry data indicate very little difference in survival between those with known and incidental malignancies. One, 3, and 5-year survival for the known malignancy group was 81.04%, 66.23% and 57.02% respectively, while incidental malignancies showed 81.6%, 68.75% and 59.3% survival. The comparison between the known malignancy group and other liver transplant recipients, however, shows larger differences in long-term survival between the groups. Among patients who are transplanted for non-malignant diseases, the 1, 3, and 5-year survival is 84%, 77.79% and 72.61% respectively. It is important to note that only 72.8% of the malignancy group are HCC patients. The Scientific Registry does not include staging data. The commingling of other types of malignancies with HCC and failure to carefully select patients may have contributed to the significant differences in long-term survival in this analysis, which appear to conflict with the medical literature reporting of better survival data for transplantation for HCC in carefully selected patients.

C. OPTN Policy

Section 1138(a)(1)(B) of the Social Security Act (the Act) requires all Medicare transplant facilities to be members of and abide by the rules of the Organ Procurement and Transplantation Network (OPTN). The OPTN contract is awarded competitively by the Department of Health and Human Services (DHHS) on a 3-5 year cycle. The United Network for Organ Sharing (UNOS) has held this contract since it was first awarded. As part of the duties of the OPTN contractor, UNOS develops, in concert with the transplant community, policies related to transplantation. Generally, the OPTN policies are highly regarded by the transplant community. The policies include statements regarding the clinical conditions for patients to receive transplants. The policies can be found on the Internet at: www.unos.org/frame_Default.asp?Category=aboutbylaws.TOC

Section 3.6.4.4 of the OPTN policy related to allocation of livers allows transplantation for patients with malignancies is as follows: Patients may be assigned to medical urgency status 2B for liver transplant if

"(i) The patient has known HCC and has undergone a thorough assessment to evaluate the number and size of tumors and to rule out any extrahepatic spread and/or macrovascular involvement (i.e., portal or hepatic veins). A pre-listing biopsy is not mandatory but the lesion must meet established imaging criteria. Histological grade, the presence of encapsulation or histological classification (fibrolamellar versus non-fibrolamellar) are not considered in determining the patient's listing as a Status 2B since a pre-listing biopsy is not required. The assessment of the patient should include ultrasound of the patient's liver, a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen and chest, and a bone scan. A re-assessment of the patient must be performed at every 3 month interval that the patient is on the UNOS waiting list.

(ii) The patient has Stage I or Stage II HCC in accordance with the modified Tumor-Node-Metastasis (TNM) classification or the patient has an alpha-fetoprotein level that is rising on 3 consecutive occasions with an absolute value >/= 500 nanograms even though there is no evidence of a tumor based on imaging studies.

(iii) The patient is not a resection candidate.

A patient with HCC at Stage III or higher may continue to be considered a liver transplant candidate in accordance with each center's own specific policy or philosphy, but the patient must be listed as a Status 3, unless the candidate meets the other criteria for Status 2B or 2A."

In considering staging of the tumor, UNOS uses the modified Tumor-Node-Metastasis (TNM) classification (see attachment 1). Under this classification Stage I designates one nodule less than 1.9 cm. Stage II designates one nodule 2.0 to 5.0 cm or two or three nodules all less than 3.0 cm. Patients with no evidence of tumor based on imaging studies may also qualify if the patient has an alpha-fetoprotein level that is rising on 3 consecutive occasions with an absolute value greater than or equal to 500 nanograms.

National Coverage Decision

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Several researchers have identified tumor number and staging as adverse factors. Further, the UNOS status 2 B criteria are limited to patients with Stage I or Stage II tumors in accordance with the Tumor-Node-Metastasis (TNM) classification system. This results in Status 2 B classification only to patients with 3 or fewer nodules. We considered use of tumor numbers and staging as independent factors in establishing our conditions for coverage in the decision memorandum. However, we found that many of the researchers did not study or find any negative relationship between tumor number and outcome. Of those researchers that did study this variable, all found a negative association, but failed to identify it as being statistically significant.

More researchers studied tumor staging as a variable. Similar to tumor number, the researchers consistently found a negative association of outcome with higher staging. That is, as the stage of the tumor increased, the disease-free survival of the patients decreased. But only one researcher, Klintmalm, in his 1998 work, found this association to be statistically significant. Given the high likelihood of occurrence of other significant adverse factors, such as increased tumor size, macrovasularization and extrahepatic spread, to occur in patients with higher stage tumors, it is possible that these other factors are the cause of the negative association of increased staging with outcomes. Therefore, we have not included these factors in our conditions for coverage in the decision memorandum.

In addition, several researchers found a negative association with outcomes for bilobar distribution and microvascularization. However, the only factor identified as statistically significant was bilobar distribution in the Iwatsuki et al. study in 1991. In Iwatsuki's later research, he empirically weighted these risk factors as 3.1 for bilobar distribution and 4.4 for microvascularization. We note that the UNOS status 2 B criteria do not consider either of these factors. Further, identification of microvascularization prior to transplantation requires the use of a biopsy procedure that, in and of itself, may be an adverse risk factor in patients with HCC in that the procedure may seed the tumor. Thus, we concluded that a link between these factors and poor outcomes is unlikely. Consequently, we did not exclude patients with these conditions from our conditions for coverage in the decision memorandum.

In summary, we have decided to issue this decision memorandum announcing our intention to revise the NCD relating to liver transplantation for malignancies. We will issue a revision to the Coverage Issues Manual stating that liver transplantation may be covered for patients with HCC when the following conditions are met:

- The patient is not a liver resection candidate;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

Liver transplantation for other malignancies continues to be excluded from coverage at this time. We will, however, seek a technology assessment on these other types of malignancies.

HCFA's coverage policies are updated as new scientific information becomes available. We welcome comments on this document now or in the future. In addiiton, HCA will accept a request for reconsideration of this decision memorandum or any NCD if there is felt to be a Federal misinterpretation of existing evidence or if new evidence is provided that may alter the conclusion of this assessment.

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Attachment 1
American Liver Tumor Study Group
Modified Tumor-Node-Metastasis (TNM) Staging Classification

Stage I	One nodule less than 1.9 cm
Stage II	One nodule 2.0-5.0 cm Two or three nodules, all less than 3.0 cm
Stage III	One nodule greater than 5.0 cm Two or three nodules, at least one greater than 3.0 cm
Stage IV A 1	Four or more nodules
Stage IV A 2	One or more nodules plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI or ultrasound
Stage IV B	Any regional (portal hepastis) nodes involved or any metastatic disease, including extrahepatic portal or hepatic vein involvement

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